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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/US2004/020026International filing date (day/month/year)
23.06.2004Priority date (day/month/year)
23.06.2003International Patent Classification (IPC) or both national classification and IPC
A61K39/385Applicant
BAXTER INTERNATIONAL INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

10/562256

International application No.
PCT/US2004/020026

IAP20 Rec'd PCT/PTO 21 DEC 2005

Box No. 1 Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
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International application No.
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Box No. II Priority

1. ☐ The following document has not been furnished:

☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US2004/020026**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 1-10 in respect of i.a.

because:

- ☒ the said international application, or the said claims Nos. 1-10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- | | |
|----------------------------|--|
| the written form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/US2004/020026

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1
	No: Claims	6, 11
Inventive step (IS)	Yes: Claims	
	No: Claims	1-15
Industrial applicability (IA)	Yes: Claims	11-15
	No: Claims	

2. Citations and explanations**see separate sheet**

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)**see form 210**

IAP20 Rec'd PCT/PTO 21 DEC 2005**Re Item III.**

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy:

Claims 1-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

1 The following documents are referred to in this communication:

- D1: US-A-5 443 966 (MAKOFF ANDREW J ET AL) 22 August 1995 (1995-08-22)
- D2: WO 99/15671 A (CHATFIELD STEVEN NEVILLE ; MEDEVA EUROP LTD (GB)) 1 April 1999 (1999-04-01)
- D3: US-A-5 785 973 (PILLAI SUBRAMONIA ET AL) 28 July 1998 (1998-07-28)
- D4: EP-A-0 427 347 (ENIRICERCHE SPA) 15 May 1991 (1991-05-15)
- D5: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 14 October 2003 (2003-10-14), KIM J ET AL: "Tetanus toxin C-fragment as a universal carrier protein for conjugate vaccines." Database accession no. PREV200400041633

Novelty (Art. 33(2) PCT) and Inventive Step (Art. 33(3) PCT).

The present invention provides immunogenic conjugate vaccines utilizing Fragment C (Amino acids 865-1315) of the tetanus toxin as carrier protein conjugated to a carbohydrate antigen (a polysaccharide from a bacterium).

Prior art:

D1 publishes a process for producing fragment C of tetanus toxin and a vaccine which comprises fragment C and may include other antigens to provide a multi-valent vaccine (see column 3, lines 20-24).

D2 publishes a vaccine comprising a polypeptide comprising tetanus toxin fragment C and the pre-S1 region of HVB (see claims 1 and 7).

D3 discloses an immunogenic conjugate consisting of a polysaccharide antigen covalently bound to one T-cell epitope of tetanus toxin (claims 1, 7 and 11). This document analyses fragment C and different fragments of it in order to map T-cell epitopes. From all the "big" fragments the C-fragment is found to be the best one (see column 33, lines 20-25).

D4 discloses immunogenic conjugates consisting of a universal peptide carrier corresponding to the amino acid residues 947-967 and 947-960 of the fragment C of tetanus toxin conjugated to polysaccharide molecules (see page 3, lines 6-14 and page 6, lines 19-26).

The subject-matter of claims 6 and 11, which does not limit the antigen to any particular one, is not novel in view of D1 and D2.

The subject-matter of claim 1, which further defines the antigen as a carbohydrate, does not appear to involve an inventive step in view of D1 or D2 in combination with any of D3-D4, the reasons being as follows:

Fragment C of the tetanus toxin is a well-known carrier for vaccines (see D1-D4), D1-D2 publish conjugates of it with antigens, although polysaccharides are not explicitly mentioned in these documents it is evident in reading D3-D4, which go even further by fragmenting Fragment C, that conjugates of fragment C with polysaccharides are feasible and convenient as alternative to TT (as it is discussed with detail in D3). Moreover, conjugates of polysaccharides of bacteria with fragment C of TT are implicitly disclosed in D3-D4 which even look for better alternatives to fragment C by fragmenting this one.

Dependent claims 2-5, 7-10 and 12-15 do not contain any feature which could render the subject-matter of the independent claims from which they depend inventive.

Industrial Applicability (Art. 33(4) PCT).

For the assessment of the present claims 1-10 on the question whether they are

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AUTHORITY (SEPARATE SHEET)

International application No.

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industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

D5 publishes the present invention after the priority date of the present application. In case that the priority date would not be valid, D5 would be considered relevant for the novelty of claims 1-15.